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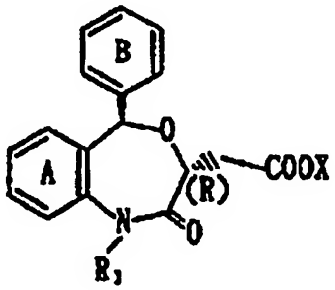
(54) Title: OPTICALLY ACTIVE 4,1-BENZOXAZEPINE DERIVATIVES USEFUL AS SQUALENE SYNTHASE INHIBITORS

(57) Abstract

Disclosed is an optically active 4,1-benzoxazepin-2-one derivative of formula (I), wherein R_1 represents a lower alkyl group; X represents a hydrogen atom or a metal ion; ring A represents a phenyl group substituted with halogen; ring B represents a phenyl group substituted with a lower alkoxy, which is useful for the prophylaxis or treatment of hypercholesteremia or coronary sclerosis of mammals.



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DESCRIPTION

OPTICALLY ACTIVE 4,1-BENZOXAZEPINE DERIVATIVES USEFUL AS SQUALENE SYNTHASE INHIBITORS

Technical Field

This invention relates to an optically active 4,1-benzoxazepin-2-one derivative or a salt thereof and to a squalene synthase inhibitor composition and an antimycotic composition each comprising said derivative as an active ingredient.

Background Art

It is known that hypercholesterolemia, alongside hypertension and smoking, is one of the three major risk factors of ischemic heart disease and a judicious control of the blood cholesterol level is essential to the prophylaxis and therapy of ischemic heart disease and coronary atherosclerosis.

As drugs capable of lowering the blood cholesterol level, agents adapted to capture bile acid to inhibit its absorption, typically cholestyramine and colestipol (disclosed in, for example, US Patent 4027009), and agents designed to inhibit acyl coenzyme A-cholesterol O-acyltransferase (ACAT) to depress the intestinal absorption of cholesterol, typically melinamide (disclosed in French Patent 1476569), are known. Furthermore, drugs inhibiting the biosynthesis of cholesterol are also attracting attention. Particularly, lovastatin (disclosed in US Patent 4231938), simvastatin (disclosed in US Patent 4444784) and pravastatin (disclosed in US Patent 4346227), which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are already in clinical use. However, since inhibition of HMG-CoA reductase leads to inhibition of the biosynthesis of not only cholesterol but also ubiquinones, dolichols, heme A and other factors

necessary for the body, the risk of consequent side effects is a serious concern.

Squalene synthase is an enzyme associated with an essential stage in the de novo cholesterol biosynthesis pathway. This enzyme catalizes the reductive dimerization of farnesyl pyrophosphate to synthesize squalene.

Meanwhile, a series of compounds which are expected to inhibit cholesterol biosynthesis through inhibition of squalene synthase have been disclosed in Journal of Medicinal Chemistry, Vol. 51(10), pp, 1869-1871 (1988), Japanese published unexamined patent application No. H1-213288/1989 (JP Kokai H1-213288/1989), JP Kokai H2-101088/1990, JP Kokai H2-235820/1990, JP Kokai H2-235821/1990, JP Kokai H3-20226/1991, JP Kokai H3-68591/1991, JP Kokai H3-148288/1991, USP 5,019,390, USP 5,135,935, WO 9215579, JP-Kokai H6-9668/1994, WO 9318039 and WO 9318040.

On the other hand, various compounds are known as antimycotic agents. In particular, compounds showing antimycotic activity through inhibition of squalene biosynthesis are described in JP Kokai H4-279589/1992, EP 475706, EP 494622 and EP 503520.

Referring, now, to 4,1-benzoxazepine derivatives and, more particularly, to 4,1-benzoxazepin-2-one derivatives which have a ketone group in the 2-position, compounds derivatized by substituting one hydrogen atom in the 3-position, with a different atomic group are disclosed in JP Kokai S57-35576/1982 and Chem. Pharm. Bull. 34, 140 (1986).

Furthermore, EP 567026 discloses certain 4,1-benzoxazepin-2-one derivatives.

It is known that ubiquinones, dolichols, heme A and other factors are biosynthesized from farnesyl pyrophosphate in the cholosterol biosynthesis pathway and, therefore, in order to avoid side effects arising

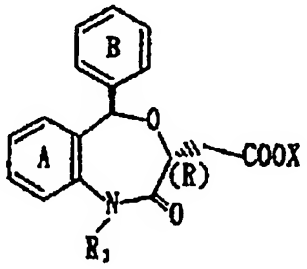
from their deficiencies, it appears to be a worthwhile attempt to inhibit enzymes subsequent to farnesyl pyrophosphate, particularly squalene synthase.

Disclosure of Invention

Under the circumstances described above the inventors of this invention did much research and discovered that an optically active 4,1-benzoxazepin-2-one derivative has excellent squalene synthase inhibiting activity. This invention has been developed on the basis of the above finding.

This invention, therefore, relates to

(1) an optically active 4,1-benzoxazepin-2-one derivative of the following formula (I)



(I)

wherein R_1 represents a lower alkyl group; X represents a hydrogen atom or a metal ion; ring A represents a phenyl group substituted with halogen; ring B represents a phenyl group substituted with a lower alkoxy;

(2) a squalene synthase inhibitor composition comprising a compound of formula (I) as an active ingredient,

(3) an antimycotic composition comprising a compound of formula (I) as an active ingredient,

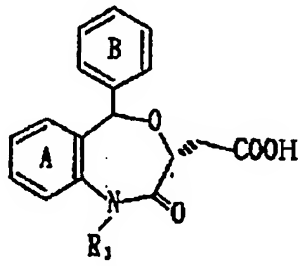
(4) a method for the prophylaxis or treatment for hypercholesterolemia or coronary sclerosis in a mammal which comprises administering a pharmaceutical effective amount of a compound of formula (I), to a mammal is need thereof,

(5) a method for the prophylaxis or treatment for mycotic diseases in a mammal which comprises administering a pharmaceutical effective amount of a compound of formula (I), to a mammal in need thereof,

(6) use of a compound of formula (I), for the manufacture of a medicament to be used as a prophylactic or therapeutic drug for hypercholesterolemia or coronary sclerosis,

(7) use of a compound of formula (I), for the manufacture of a medicament to be used as a prophylactic or therapeutic drug for mycotic diseases,

(8) a method for producing a compound of formula (I) which comprises (i) subjecting a compound of the following formula:



wherein all symbols are of the same meanings as above, to optical resolution and (ii), if necessary, dissolving the resultant compound and an alkali metal hydroxide in an alcoholic solvent, and

(9) The method according to the above-mentioned (8), which comprises reacting the compound with an optically active amine.

Best Mode for Carrying Out the Invention

The invention further provides a production technology for novel compounds which was fallen under the purview of formula (I).

Referring to the formula (I) of this invention, the substituent groups in the 3- and 5-positions are oriented trans to each other, viz. in opposite directions, with respect to the plane of the 7-membered

ring and (R) stands for R-configuration.

Referring, further, to formula (I), the lower alkyl group indicated by the symbol R_1 includes straight-chain or branched C_{1-7} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, 1-ethylpropyl, etc. and is preferably a C_{4-5} alkyl group and most desirably isobutyl or neopentyl.

The metal ion indicated by the symbol X includes sodium ion, potassium ion, calcium ion and aluminum ion, among others, and is preferably sodium ion or potassium ion.

The halogen atom of the halogen-substituted phenyl group, represented as ring A, includes fluorine, chlorine, bromine and iodine and is preferably chlorine.

The lower alkoxy group of the lower alkoxy-substituted phenyl group, represented as ring B, includes straight-chain or branched C_{1-6} alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, etc. and is preferably a C_{1-4} alkoxy group and most desirably methoxy or ethoxy.

Practical examples of the compounds of this invention are disclosed as follows:

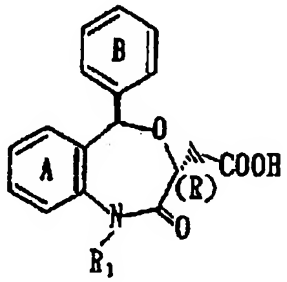
(3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium salt,

(3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium salt,

(3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-

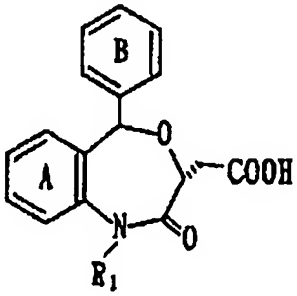
acetic acid or its sodium salt.

Among compounds of formula (I), compounds of the following formula (Ia)



(Ia)

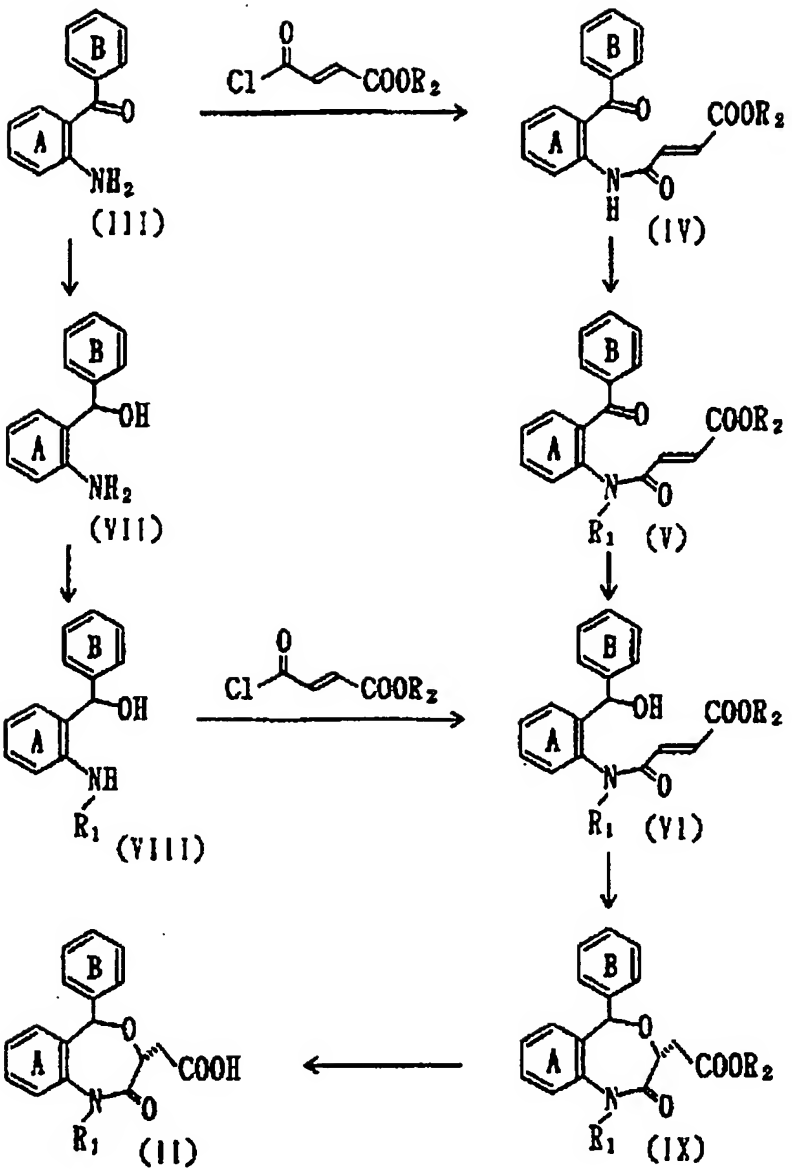
wherein R_1, ring A and ring B are as defined hereinbefore, can be produced by subjecting the corresponding compounds of the following formula (II) to optical resolution.



(II)

wherein all the symbols have the meanings defined hereinbefore.

Compounds of formula (II) can be produced by the following processes as described in EP 567026. Incidentally the starting compound 2-aminobenzophenone can be synthesized by any of the processes described in D. A. Walsh: Synthesis 677, 1980, the processes referred to in the same literature, and processes analogous thereto.



wherein R_2 represents an alkyl or aralkyl group of 1-8 carbon atoms; the other symbols have the meanings defined hereinbefore.

The reaction from (III) to (IV) and that from (VIII) to (VI) can be respectively carried out by utilizing the per se known acylation procedures. For example, the acylation reaction for purposes of this invention can be carried out in a solvent, typically an

ether such as diethyl ether, tetrahydrofuran, dioxane, etc., a halogen-containing solvent such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc., a hydrocarbon solvent such as benzene, toluene, hexane, heptane, etc., dimethylformamide or dimethyl sulfoxide, where necessary in the presence of water and a base, typically an organic base such as 4-dimethylaminopyridine, triethylamine, triethylenediamine, tetramethylethylenediamine, etc., or an inorganic base such as sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, etc., sodium hydride, potassium hydride and so on. Relative to each mole of (III) or (VIII), fumaric acid chloride monoalkyl or aralkyl ester is used in a proportion of generally about 1-10 moles and preferably about 1-3 moles. The reaction time is generally about 1-48 hours and preferably about 5-10 hours. The reaction temperature is generally about -50 to 100°C and preferably about 0-50°C.

The reaction from (III) to (VII) and that from (V) to (VI) can respectively be carried out by treating the starting compound with a metal hydrogen complex compound, typically lithium aluminum hydride, sodium aluminum hydride, sodium triethoxyaluminum hydride, sodium borohydride, etc., in a protic solvent such as methanol, ethanol, propanol, butanol, etc. or an aprotic solvent such as ethyl ether, tetrahydrofuran, dioxane and so on. The metal hydride complex compound is used in a proportion of generally 0.3-5 moles and preferably 0.5-2 moles per mole of (III) or (V). The reaction temperature is generally about -20 to 100°C and preferably about 20-50°C.

The reaction from (VII) to (VIII) and that from (IV) to (V) can respectively be carried out by

permitting an alkyl halide, typically neopentyl chloride, neopentyl bromide, neopentyl iodide, isobutyl chloride, isobutyl bromide or isobutyl iodide, to act on (VII) or (IV) in a solvent, e.g. ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., hydrocarbons such as benzene, toluene, hexane, heptane, etc., alcohols such as methanol, ethanol, propanol, butanol, etc., acetone, dimethylformamide, etc., where necessary in the presence of a base such as sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride and so on. Relative to each mole of (VII) or (IV), the alkyl halide is used in a proportion of generally about 1-10 moles or preferably about 1-2 moles. The reaction temperature is about 0-100°C and preferably about 20-50°C. The reaction time is generally about 1-24 hours and preferably about 3-10 hours.

Production of (VIII) from (VII) can also be carried out in the manner of catalytic reduction by using Pd or Pd on activated carbon as the catalyst or in the manner of reductive amination in the presence of sodium borohydride or sodium cyanoborohydride between compound (VII) and straight-chain or branched alkyl aldehydes and ketones such as formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, trimethylacetaldehyde, acetone, 2-butanone, etc. in a solvent, e.g. ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., hydrocarbons such as benzene, toluene, hexane, heptane, etc., and alcohols such as methanol, ethanol, propanol, butanol, etc. Relative to each mole of (VII), the aldehyde is used in a proportion of generally 1-10 moles and preferably 1-2 moles and the reducing agent is used in a proportion of 0.3-5 moles or preferably 0.5-1 mole. The reaction temperature is 0-100°C and

preferably 10 - 30°C. The reaction time is generally about 1-24 hours and preferably about 3-10 hours.

The reaction from (VI) to (IX) can be carried out in a solvent, e.g. ethers such as diethyl ether, tetrahydrofuran, dioxane, etc., hydrocarbons such as benzene, toluene, hexane, heptane, etc., alcohols such as methanol, ethanol, propanol, butanol, etc., acetone, and dimethylformamide, where necessary in the presence of a base such as sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium hydride, potassium hydride and so on. Relative to each mole of compound (VI), the base is used in a proportion of generally about 1-5 moles and preferably about 1-2 moles. The reaction temperature is generally -20 to 200°C and preferably 20-100°C. The reaction time is generally 1-20 hours and preferably about 2-5 hours.

The reaction from (IX) to (II) can be carried out by treating (IX) with an acid or a base. For example, this reaction can be carried out in an aqueous solution of mineral acid (e.g. nitric acid, hydrochloric acid, hydrobromic acid, iodic acid, sulfuric acid, etc.) or alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide, etc.) at a temperature of 0-150°C, preferably 20-50°C. The proper strength of the acid or base is about 1-10 normal, preferably 4-10N. The reaction time, which depends on the reaction temperature, is generally about 1-24 hours and preferably about 2-10 hours.

The optical resolution of compound (II) can be carried out by reacting compound (II) with an optically active amine.

The optical resolution of compound (II) can be carried out by reacting compound (II) with an optically active amine, such as an amino acid (e.g. alanine, valine, leucine, isoleucine, serine, threonine, lysine,

phenylalanine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, methionine, etc.) whose carboxyl function has been esterified with an alkyl or aralkyl group of 1-8 carbon atoms, subjecting the resulting amide to distillation, recrystallization, column chromatography or other procedure to fractionate the desired optical isomer and cleaving the amide linkage to provide the object compound (Ia).

The amide mentioned above can be synthesized by condensing compound (II) with said amino acid ester using a condensing agent in a solvent, where necessary in the presence of a base. The solvent that can be used includes hydrocarbons such as benzene, toluene, hexane, heptane, etc., halogen-containing solvents such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc., ethers such as ethyl ether, tetrahydrofuran, dioxane, etc., acetonitrile, dimethylformamide and so on. The base may for example be triethylamine, 4-dimethylaminopyridine, triethylenediamine, or tetramethylethylenediamine. The condensing agent includes those used in peptide synthesis, such as dicyclohexylcarbodiimide, diethyl cyanophosphonate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and so on. Relative to each mole of compound (II), the amino acid ester is used generally in a proportion of 0.5-2 molar equivalents, preferably 1-1.2 molar equivalents, and the condensing agent is used in a proportion of 0.5-5 molar equivalents, preferably 1-2 molar equivalents. The reaction temperature is 0-100°C and preferably 20-50°C. The reaction time is 0.5-24 hours and preferably about 1-5 hours.

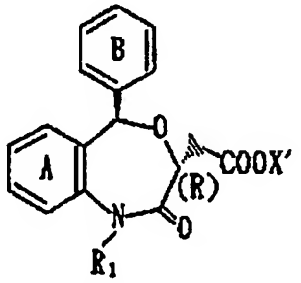
Cleavage of the amide linkage can be carried out in a solvent, such as water, methanol, ethanol, propanol, butanol, etc., in the presence of an alkali metal hydroxide (e.g. sodium hydroxide, potassium

hydroxide, barium hydroxide, lithium hydroxide, etc.), sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, etc., or in the presence of a mineral acid (e.g. nitric acid, hydrochloric acid, hydrobromic acid, iodic acid, sulfuric acid, etc.) at a temperature of 10-150°C, preferably 10-50°C. The reaction time which depends on the reaction temperature is generally 1-24 hours and preferably about 2-10 hours.

Also, the optical resolution of compound (II) can be carried out by reacting compound (II) with an optically active amine (e.g. quinine, cinchonidine, brucine, dehydroabiethylamine, nicotine, etc.) and subjecting the resulting salt to fractional crystallization to provide the object compound (Ia).

As an alternative, compound (Ia) can be produced after optical resolution of compound (VII) or (VIII).

Among the compounds of formula (I), the compound of formula (Ib)



(Ib)

wherein X' represents a metal ion and the other symbols have the same meanings as defined hereinbefore, can be produced by dissolving compound (Ia) and an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.) in equimolar proportions in an alcoholic solvent such as methanol, ethanol, propanol or butanol.

While the compound (I) of this invention has squalene synthase inhibitory activity, some species have activity to inhibit other enzymes, as well, in the

cholesterol biosynthesis pathway. In any event, the compound (I) of this invention inhibits the biosynthesis of cholesterol and is, therefore, useful for the prevention and therapy of hypercholesterolemia and coronary atherosclerosis in mammalian animals (e.g. mouse, rat, rabbit, dog, cat, bovine, swine, man, etc.).

For use of the compound in man, it can be administered orally or by other routes. The composition for oral administration includes solid and liquid dosage forms such as tablets (inclusive of dragees, film-coated tablets, etc.), pills, granules, powders, capsules (inclusive of soft capsules), syrups, emulsions, suspensions, and so on. These compositions can be manufactured by per se known procedures and generally contain some carrier or vehicle which is conventionally used in the pharmaceutical field. Taking the carrier for tablet use as an example, lactose, starch, sucrose, magnesium stearate, etc. can be mentioned.

Typical compositions for administration by other routes are injections and suppositors. The former includes subcutaneous, intradermal and intramuscular injections, among others. Such injections can be manufactured by suspending or emulsifying the compound of this invention in a sterile aqueous or oily vehicle which is conventionally used. The aqueous vehicle for injection includes physiological saline or other isotonic solution and may contain a suitable suspending agent such as carboxymethylcellulose sodium, a nonionic surfactant or the like. The oily vehicle includes sesame oil and soybean oil as typical examples and may contain a solubilizer such as benzyl benzoate, benzyl alcohol, etc. The injection so prepared is filled in appropriate ampules.

The compound (I) has only a low toxic potential

which provides for safe use. While the daily dosage is dependent on the patient's clinical condition and body weight, species of the compound, route of administration, etc., the recommended daily dose as an antihypercholesterolemic agent for an adult is about 1-500 mg, preferably about 10-200 mg, for an oral regimen and about 0.1-100 mg, preferably about 1-20 mg, for administration by other routes (e.g. in the case of an injection or a suppository). Within the above-mentioned dose range, no toxic reactions have been observed.

Furthermore, the compound (I) has a broad antimicrobial spectrum as assayed by the broth or agar dilution assay.

For use of compound (I) as a therapeutic agent for mycotic diseases (e.g. in man), the effective daily dose for an adult is about 0.1-100 mg, preferably about 1-50 mg, for oral administration and about 0.1-100 mg, preferably 1-50 mg for administration by other routes (e.g. in the case of an injection or a suppository). For the treatment of mycotic infection, the unit dose of 2-5 mg/kg can be generally employed.

Examples

The following examples, formulation examples and test examples are now presented to illustrate this invention in further detail and should by no means be construed as defining the scope of the invention.

Example 1

(3S,5R)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (I) and (3R,5S)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (II)

(1) N-[(3S,5R)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester and N-[3R,5S)-7-

chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester

Trans-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (3.0 g) and L-alanine tert-butyl ester hydrochloride (1.51 g) were dissolved in dimethylformamide (20 ml), and after the solution was cooled to 0°C, diethyl cyanophosphonate (1.43 g) and triethylamine (2.42 ml) were added. The mixture was stirred at room temperature for 30 minutes, after which it was diluted with water and extracted with ethyl acetate (50 ml). The extract was washed with 1N-HCl (20 ml x 2) and a saturated aqueous solution of sodium hydrogen carbonate (20 ml x 2) and dried over anhydrous magnesium sulfate. The solvent was then removed and the residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate = 3:1 - 1:1). As a result, 1.55 g of N-[(3S,5R)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester was obtained as a first eluate. Colorless crystals (m.p. 94-97°C).

Elemental analysis for $C_{30}H_{39}ClN_2O_6$

Calcd.: C, 64.55; H, 7.03; N, 5.01

Found : C, 64.05; H, 7.27; N, 4.72

In addition, 1.8 g of N-[(3R,5S)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester was obtained as a second eluate. An oil.

^{1}H-NMR ($CDCl_3$) δ: 0.93 (9H, s), 1.35 (3H, d, J=7.0 Hz), 1.45 (9H, s), 2.69 (1H, dd, J=14.6, 5.7 Hz), 2.87 (1H, dd, J=14.4, 7.2 Hz), 3.34 (1H, d, J=14.0 Hz), 3.62 (3H, s), 4.3-4.5 (2H, m), 4.49 (1H, d, J=14.0 Hz), 6.27 (1H, s), 6.3-6.4 (1H, brd), 6.6-6.7 (1H, m), 6.8-7.7 (6H, m)

(2) N-[(3S,5R)-7-Chloro-5-(2-methoxyphenyl)-1-

neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine

N-[(3S,5R)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester (1.4 g) as obtained in (1) was dissolved in 4N-HCl in dioxane (20 ml) and the solution was stirred at room temperature for 5 hours. The reaction mixture was then diluted with water (50 ml) and extracted with ethyl acetate (50 ml). The extract was washed with water and dried over anhydrous magnesium sulfate. Finally the solvent was distilled off to provide N-[(3S,5R)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine (1.20 g) as an amorphous solid.

^{1}H-NMR ($CDCl_3$) δ: 0.93 (9H, s), 1.44 (3H, d, J=7.2 Hz), 2.71 (1H, dd, J=14.4, 5.5 Hz), 2.93 (1H, dd, J=14.4, 7.6 Hz), 3.35 (1H, d, J=13.9 Hz), 3.63 (3H, s), 4.3-4.4 (1H, m), 4.4-4.6 (2H, m), 6.27 (1H, s), 6.63 (1H, d, J=1.9 Hz), 6.71 (1H, brd, J=6.8 Hz), 6.8-7.7 (6H, m)

Elemental analysis for $C_{26}H_{31}ClN_2O_6$

Calcd.: C, 62.09; H, 6.21; N, 5.57

Found : C, 62.38; H, 6.51; N, 5.34

(3) N-[(3R,5S)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine

N-[(3R,5S)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester (1.8 g) as obtained in (1) was treated in the same manner as (2) to provide N-[(3R,5S)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine (1.35 g) as an amorphous solid.

^{1}H-NMR ($CDCl_3$) δ: 0.93 (9H, s), 1.43 (3H, d, J=7.2 Hz), 2.73 (1H, dd, J=14.6, 5.8 Hz), 2.89 (1H, dd,

J=14.6, 5.8 Hz), 3.35 (1H, d, J=14.0 Hz), 3.63 (3H, s), 4.38 (1H, t, J=7.4 Hz), 4.45-4.6 (2H, m), 6.28 (1H, s), 6.55 (1H, brd, J=6.8 Hz), 6.64 (1H, d, J=2.0 Hz), 6.8-7.7 (6H, m)

Elemental analysis for $C_{26}H_{31}ClN_2O_6$

Calcd.: C, 62.09; H, 6.21; N, 5.57

Found : C, 61.96; H, 6.23; N, 5.38

(4) (3S,5R)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (I)

N-[(3S,5R)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine (1.0 g) as obtained in (2) was dissolved in methanol (10 ml) followed by addition of concentrated hydrochloric acid (10 ml) and the mixture was refluxed for 24 hours. The reaction mixture was then diluted with water and extracted with ethyl acetate (50 ml). The extract was washed with water and dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was dissolved in dimethylformamide (20 ml) followed by addition of methyl iodide (0.19 ml) and potossium carbonate (0.55 g) and the mixture was stirred at room temperature for 1 hour. This reaction mixture was diluted with water and extracted with ethyl acetate (50 ml). The extract was washed with 1N-hydrochloric acid (20 ml x 2) and a saturated aqueous solution of sodium hydrogen carbonate (20 ml x 2) and dried over anhydrous magnesium sulfate. The solvent was then distilled off and the residue was purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 3:1) to provide methyl (3S,5R)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (0.51 g). This compound was dissolved in a mixture of water (10 ml) and methanol (10 ml) followed by addition of potassium carbonate (0.32 g) and the mixture was refluxed for 2.5

hours. The reaction mixture was then acidified with 1N-HCl (20 ml) and extracted with ethyl acetate (50 ml). The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 2:1-dichloromethane:methanol = 2:1) to provide 0.46 g of (3S,5R)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as colorless crystals (m.p. 179-183°C).

$[\alpha]_D^{25}$ + 248.7° (c=0.45, MeOH)

Elemental analysis for $C_{23}H_{26}ClNO_5 \cdot H_2O$

Calcd.: C, 61.40; H, 6.27; N, 3.11

Found : C, 61.12; H, 5.99; N, 3.28

(5) (3R,5S)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (II)

N-[(3R,5S)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine (1.0 g) as obtained in (3) was subjected to the same procedure as (4) to provide 0.32 g of (3R,5S)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as colorless crystals (m.p. 176-180°C).

$[\alpha]_D^{25}$ - 246.2° (c=0.42, MeOH)

Elemental analysis for $C_{23}H_{26}ClNO_5 \cdot 1.5H_2O$

Calcd.: C, 60.19; H, 6.37; N, 3.05

Found : C, 60.05; H, 5.88; N, 3.22

Example 2

(3S,5R)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (I) and (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (II)

Using trans-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-

acetic acid, the title compound was sythesized in the same manner as Example 1.

(1) N-[(3S,5R)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester

Colorless crystals (m.p.: 120-122°C)

Elemental analysis for $C_{31}H_{41}ClN_2O_7 \cdot 0.5H_2O$

Calcd.: C, 62.25; H, 7.08; N, 4.68

Found : C, 62.45; H, 6.89; N, 4.68

(2) N-[(3R,5S)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester

Colorless crystals (m.p.: 136-137°C)

Elemental analysis for $C_{31}H_{41}ClN_2O_7 \cdot 0.8H_2O$

Calcd.: C, 61.69; H, 7.11; N, 4.64

Found : C, 61.60; H, 7.45; N, 4.58

(3) N-[(3S,5R)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine

Colorless crystals (m.p.: 182-185°C)

Elemental analysis for $C_{27}H_{33}ClN_2O_7$

Calcd.: C, 60.84; H, 6.24; N, 5.26

Found : C, 60.78; H, 6.09; N, 4.99

(4) N-[(3R,5S)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine

Colorless crystals (m.p.: 137-140°C)

Elemental analysis for $C_{27}H_{33}ClN_2O_7 \cdot 0.3C_6H_{14} \cdot 0.3H_2O$

Calcd.: C, 61.11; H, 6.77; N, 4.95

Found : C, 61.21; H, 6.91; N, 5.05

(5) (3S,5R)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (I)

Colorless crystals (m.p.: 227-230°C)

$[\alpha]_D^{25}$ + 242.7° (c=0.41, MeOH)

Elemental analysis for $C_{24}H_{28}ClNO_6 \cdot 0.5H_2O$

Calcd.: C, 61.21; H, 6.21; N, 2.97
Found : C, 61.20; H, 6.07; N, 2.91

(6) (3R,5S)-7-Chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (II)

Colorless crystals (m.p.: 218-222°C)

$[\alpha]_D^{25}$ - 246.8° (c=0.43, MeOH)

Elemental analysis for $C_{24}H_{28}ClNO_6 \cdot 0.75H_2O$

Calcd.: C, 60.63; H, 6.25; N, 2.95
Found : C, 60.58; H, 6.05; N, 2.95

Example 3

(3S,5R)-7-Chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (I) and (3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (II)

(1) N-[(3S,5R)-7-Chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-leucine methyl ester and N-[(3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-leucine methyl ester

Trans-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (11.0 g) and L-leucine methyl ester hydrochloride (5.2 g) were dissolved in dimethylformamide (50 ml). The solution was cooled to 0°C and diethyl cyanophosphonate (4.9 g) and triethylamine (8.3 ml) were added. The mixture was stirred at room temperature for 30 minutes, after which it was diluted with water (200 ml) and extracted with ethyl acetate (300 ml). The extract was washed with 1N-hydrochloric acid (100 ml x 2) and a saturated aqueous solution of sodium hydrogen carbonate (100 ml x 2) and dried over anhydrous magnesium sulfate. The solvent was then distilled off and the residue was

purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 2:1-1:1). As a first eluate, 6.7 g of N-[(3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-leucine methyl ester was obtained as colorless crystals (m.p. 93-96°C).

Elemental analysis for $C_{31}H_{41}ClN_2O_7 \cdot 0.5H_2O$

Calcd.: C, 62.25; H, 7.08; N, 4.68

Found : C, 62.38; H, 7.42; N, 4.43

As a second eluate, 6.5 g of N-[(3S,5R)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-leucine methyl ester was obtained as oil.

^{1}H-NMR ($CDCl_3$) δ: 0.8-1.1 (15H, m), 1.5-1.75 (1H, m), 2.70 (1H, dd, J=14.4, 6.0 Hz), 2.88 (1H, dd, J=14.4, 6.6 Hz), 3.35 (1H, d, J=14.0 Hz), 3.60 (3H, s), 3.71 (3H, s), 3.86 (3H, s), 4.33 (1H, t, J=6.2 Hz), 4.51 (1H, d, J=14.0 Hz), 4.5-4.7 (1H, m), 6.21 (1H, m), 6.45-6.7 (4H, m), 7.2-7.6 (3H, m).

(2) (3S,5R)-7-Chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (I)

N-[(3S,5R)-7-Chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-leucine methyl ester (1.0 g) as obtained in (1) was dissolved in methanol (20 ml) followed by addition of concentrated sulfuric acid (4 ml) and the mixture was refluxed for 24 hours. The reaction mixture was then diluted with water and extracted with ethyl acetate (50 ml). The extract was washed with water and dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 5:1) to provide methyl (3S,5R)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-

1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (0.22 g). This compound was dissolved in a mixture of water (10 ml), methanol (10 ml) and tetrahydrofuran (5 ml) followed by addition of potassium carbonate (0.13 g) and the mixture was refluxed for 2 hours. The reaction mixture was then acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous magnesium suflate and the solvent was distilled off to provide 0.20 g of (3S,5R)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as colorless crystals (m.p. 233-234°C).

$[\alpha]_D^{22}$ + 228.1° (c=0.51, MeOH)

Elemental analysis for $C_{24}H_{28}ClNO_6$

Calcd.: C, 62.40; H, 6.11; N, 3.03

Found : C, 62.28; H, 6.41; N, 2.89

(3) (3R,5S)-7-Chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (II)

Using N-[(3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-leucine methyl ester (6.0 g) as obtained in (1), the procedure of (2) was otherwise repeated to provide 0.7 g of (3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as colorless crystals (m.p. 234-235°C).

$[\alpha]_D^{25}$ - 232.5° (c=0.41, MeOH)

Elemental analysis for $C_{24}H_{28}ClNO_6$

Calcd.: C, 62.40; H, 6.11; N, 3.03

Found : C, 62.39; H, 6.20; N, 2.81

Example 4

Sodium (3R,5S)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

(3R,5S)-7-Chloro-5-(2-methoxyphenyl)-1-neopentyl-

2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (12 g) as obtained in Example 1 was suspended in methanol (250 ml) and dissolved by adding 1N-aqueous sodium hydroxide (27.7 ml). After the solvent was distilled off under reduced pressure, ethyl acetate (200 ml) was added to the residue and the solvent was distilled off under reduced pressure. This procedure was performed a second time and the resulting crystals were treated with ethyl acetate and filtered to provide 11.8 g of sodium (3R,5S)-7-chloro-5-(2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as colorless crystals (m.p. >300°C).

$[\alpha]_D^{22}$ - 263.6° (c=0.64, MeOH)

Elemental analysis for $C_{23}H_{25}ClNO_5Na \cdot 0.75H_2O$

Calcd.: C, 59.10; H, 5.71; N, 3.00

Found : C, 59.27; H, 5.97; N, 2.75

Example 5

Sodium (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

Using (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (30 g), the procedure of Example 4 was otherwise repeated to provide 31.9 g of sodium (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as colorless crystals (m.p. >300°C).

$[\alpha]_D^{23}$ - 235.1° (c=0.60, MeOH)

Elemental analysis for $C_{24}H_{27}ClNO_6Na \cdot 1.5H_2O$

Calcd.: C, 56.42; H, 5.92; N, 2.74

Found : C, 56.49; H, 6.02; N, 2.75

Example 6

Sodium (3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

Using (3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-

neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (24 g), the procedure of Example 4 was otherwise repeated to provide 24.7 g of sodium (3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as colorless crystals (m.p. >300°C).

$[\alpha]_D^{23}$ - 231.1° (c=0.70, MeOH)

Elemental analysis for $C_{24}H_{27}ClNO_6Na \cdot 0.75H_2O$

Calcd.: C, 57.95; H, 5.78; N, 2.82

Found : C, 57.86; H, 6.08; N, 2.81

Example 7

Trans-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

(1) 2-Amino-4'-benzyloxy-5-chloro-2'-methoxybenzophenone

A mixture of 4-bromo-3-methoxyphenol (21 g), benzyl bromide (13.5 ml), potassium carbonate (21.4 g) and acetone (200 ml) was stirred at room temperature for 24 hours. The insoluble matter was then filtered off and the filtrate was distilled under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 20:1) to provide 4-benzyloxy-2-methoxybromobenzene (25 g) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s), 5.04 (2H, s), 5.04 (2H, s), 6.47 (1H, dd, J=8.6, 2.6 Hz), 6.57 (1H, d, J=2.6 Hz), 7.3-7.5 (8H, m).

Starting with this compound, the process described in L. H. Sternbach et al.: J. Org. Chem., 27, 378, 1962 was followed to provide 20.4 g of 2-amino-4'-benzyloxy-5-chloro-2'-methoxybenzophenone as light-yellow crystals (m.p. 97-98°C).

Elemental analysis for $C_{21}H_{18}ClNO_3$

Calcd.: C, 68.57; H, 4.93; N, 3.81

Found : C, 68.62; H, 5.09; N, 3.65

(2) 2-Amino-α-(4-benzyloxy-2-methoxyphenyl)-5-chlorobenzyl alcohol

2-Amino-4'-benzyloxy-5-chloro-2'-methoxybenzophenone (10 g) was dissolved in methanol (100 ml) followd by addition of sodium borohydride (1.4 g) and the mixture was stirred for 24 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water (200 ml) and extracted with ethyl acetate (300 ml). The extract was washed with water and dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 4:1-2:1) to provide 9.5 g of 2-amino-α-(4-benzyloxy-2-methoxyphenyl)-5-chlorobenzyl alcohol as colorless crystals (m.p. 101-103°C).

Elemental analysis for $C_{21}H_{20}ClNO_3$

Calcd.: C, 68.20; H, 5.41; N, 3.79

Found : C, 67.97; H, 5.42; N, 3.58

(3) α-(4-Benzyloxy-2-methoxyphenyl)-2-neopentylamino-5-chlorobenzyl alcohol

A mixture of 2-amino-α-(4-benzyloxy-2-methoxyphenyl)-5-chlorobenzyl alcohol (9.5 g), pivalaldehyde (3.35 ml), acetic acid (1.85 g) and ethanol (200 ml) was stirred at room temperature for 30 minutes. Then, sodium cyanoborohydride (2.33 g) was added and the mixture was stirred for 24 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water (200 ml) and extracted with ethyl acetate (200 ml). The extract was washed with water and dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 5:1) to provide α-(4-benzyloxy-2-methoxyphenyl)-2-neopentylamino-5-chlorobenzyl alcohol (10 g) as

colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 0.91 (9H, s), 2.82 (2H, s), 3.10 (1H, br), 3.85 (3H, s), 4.75 (1H, br), 5.06 (2H, s), 5.94 (1H, s), 6.45-6.7 (3H, m), 6.95-7.5 (7H, m)

(4) Ethyl 3-[N-[4-chloro-2-(4-benzyloxy-α-hydroxy-2-methoxybenzyl)phenyl]-N-neopentylcarbamoyl]acrylate

α-(4-Benzyloxy-2-methoxyphenyl)-2-neopentylamino-5-chlorobenzyl alcohol (10 g) in dichloromethane (200 ml) was added sodium hydrogen carbonate (6.3 g) and while the mixture was stirred, fumaric acid monochloride monoethyl ester (4.43 g) was added dropwise. The mixture was stirred at room temperature for 30 minutes. This reaction mixture was washed with water and dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane:ethyl acetate = 5:1-2:1) to provide ethyl 3-[N-[4-chloro-2-(4-benzyloxy-α-hydroxy-2-methoxybenzyl)phenyl]-N-neopentylcarbamoyl]-acrylate (12 g) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 0.7-1.0 (9H, m), 1.1-1.3 (3H, m), 2.5-3.15 (2H, m), 3.69, 3.77 (3H, each s), 3.9-4.5 (3H, m), 4.95, 5.07 (2H, each s), 5.9-6.85 (5H, m), 6.95-7.9 (10H, m)

(5) Ethyl trans-7-chloro-5-(4-benzyloxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

To a solution of ethyl 3-[N-[4-chloro-2-(4-benzyloxy-α-hydroxy-2-methoxybenzyl)phenyl]-N-neopentylcarbamoyl]acrylate (12 g) in ethanol (150 ml) was added potassium carbonate (5.9 g) and the mixture was stirred for 24 hours. The solvent was then distilled off under reduced pressure and the residue was diluted with water (200 ml) and extracted with ethyl acetate (200 ml). The extract was washed with water and dried over anhydrous magnesium sulfate and

the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane:ethyl acetate = 3:1) to provide 9.8 g of ethyl trans-7-chloro-5-(4-benzyloxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as colorless crystals (m.p. 130-131°C).

Elemental analysis for $C_{32}H_{36}ClNO_6$

Calcd.: C, 67.90; H, 6.41; N, 2.47

Found : C, 67.73; H, 6.35; N, 2.33

(6) Ethyl trans-7-chloro-5-(4-hydroxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxyazepine-3-acetate

In ethyl acetate (150 ml) was dissolved ethyl trans-7-chloro-5-(4-benzyloxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxyazepine-3-acetate (7.0 g) followed by addition of 1N-HCl (0.1 ml) and 10% palladium-on-carbon (50% hydrous, 1.0 g) and the catalytic reduction reaction was carried out at room temperature under atmospheric pressure. After a stoichiometric amount of hydrogen had been absorbed, the palladium-on-carbon was filtered off and the filtrate was distilled under reduced pressure to recover 5.6 g of ethyl trans-7-chloro-5-(4-hydroxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as colorless crystals (m.p. 197-199°C).

Elemental analysis for $C_{25}H_{30}ClNO_6$

Calcd.: C, 63.09; H, 6.35; N, 2.94

Found : C, 62.97; H, 6.57; N, 2.81

(7) Ethyl trans-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

A mixture of ethyl trans-7-chloro-5-(4-hydroxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (0.25 g), ethyl iodide

(0.06 ml), potassium carbonate (0.15 g) and N,N-dimethylformamide (20 ml) was stirred at room temperature for 3 hours. The reaction mixture was then diluted with water (50 ml) and extracted with ethyl acetate (100 ml). The extract was washed with 1N-HCl (30 ml x 2) and a saturated aqueous solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure to provide 0.24 g of ethyl trans-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as colorless crystals (m.p. 164-166°C).

Elemental analysis for $C_{27}H_{34}ClNO_6$

Calcd.: C, 64.34; H, 6.80; N, 2.78

Found : C, 64.18; H, 6.70; N, 2.74

(8) trans-7-Chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

A mixture of ethyl trans-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate (0.18 g), potassium carbonate (0.1 g), methanol (10 ml), tetrahydrofuran (10 ml) and water (5 ml) was refluxed for 1.5 hours. The reaction mixture was then concentrated under reduced pressure, 1N-HCl (50 ml) was added, and the mixture was extracted with ethyl acetate (50 ml). The extract was washed with water and dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure to provide 0.15 g of trans-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as colorless crystals (m.p. 230-232°C).

Elemental analysis for $C_{25}H_{30}ClNO_6$

Calcd.: C, 63.09; H, 6.35; N, 2.94

Found : C, 62.92; H, 6.60; N, 3.01

Example 8

(3R,5S)-7-Chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid

In the same manner as Example 1, trans-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (2.2 g) was reacted with L-alanine tert-butyl ester and the reaction product purified by silica gel column chromatography to provide N-[(3S,5R)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester (1.0 g) and N-[(3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester (1.1 g).

Repeating the procedure described in Example 1 (2), N-[(3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetyl]-L-alanine tert-butyl ester (0.8 g) was reacted to provide 0.33 g of (3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid as colorless crystals (m.p. 162-165°C).

Elemental analysis for $C_{25}H_{30}ClNO_6$

Calcd.: C, 63.09; H, 6.35; N, 2.94

Found : C, 62.87; H, 6.23; N, 2.66

$[\alpha]_D^{23}$ - 212.0° (c=0.94, MeOH)

Example 9

Sodium (3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

Using (3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (3.65), the procedure of Example 4 was repeated to provide 3.54 g of sodium (3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-

neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-penzoxazepine-3-acetate as colorless crystals (230-250°C, decomp.).

Elemental analysis for $C_{25}H_{29}ClNO_6Na \cdot 0.7H_2O$

Calcd.: C, 58.81; H, 6.00; N, 2.74

Found : C, 58.91; H, 6.24; N, 2.71

$[\alpha]_D^{23}$ - 218.8° (c=0.48, MeOH)

Reference Example 1

Sodium (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate

Starting with (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid (1.2 g) as described in Example 118 of EP 567026, the procedure of Example 4 was otherwise repeated to provide 1.1 g of sodium (3R,5S)-7-chloro-5-(2-chlorophenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetate as colorless crystals (m.p. >300°C).

$[\alpha]_D^{22}$ - 237.1° (c=0.57, MeOH)

Elemental analysis for $C_{22}H_{22}Cl_2NO_4Na \cdot H_2O$

Calcd.: C, 55.47; H, 5.08; N, 2.94

Found : C, 55.41; H, 5.26; N, 2.83

Assay of squalene synthase inhibitory activity

Squalene synthase inhibitory activity is assayed by the following method using the enzyme preparations described in Test Examples 1 and 2.

To a solution containing 5 μM[1-^{3}H] farnesyl pyrophosphate (specific activity 25 μCi/mole), 1 mM NADPH (nicotinamide adenine dinucleotide phosphate, reduced form), 5mM $MgCl_2$, 6 mM glutathione, 100 mM potassium phosphate buffer (pH 7.4) and the test drug (dissolved in water or DMSO) (total volume: 50 μl) is added the enzyme solution (0.8 μg protein) prepared in Test Example 1 or 2 and the reaction is carried out at 37°C for 45 minutes. The reaction is stopped by adding 150 μl of chloroform-methanol (2:1) followed by addition of 50 μl of chloroform and 50 μl of 3N-sodium

hydroxide solution. The chloroform layer (bottom layer, 50 µl) containing the reaction product composed predominantly of squalene is mixed with 3 ml of toluenic liquid scintillator and its radioactivity was measured using a liquid scintillation counter.

The squalene synthase inhibitory activity was expressed in the concentration which caused 50% inhibition of the radioactivity uptake by the chloroform layer [IC_{50}, molar concentration (M)].

Test Example 1 Preparation of a rat enzyme

A male SD rat (6 weeks old) is bled to death and the liver is enucleated. About 10 g of the heptic tissue was washed with ice-cooled saline and homogenized in 15 ml of ice-cooled buffer [100 mM potassium phosphate buffer (pH 7.4), 15 mM nicotinamide, 2mM $MgCl_2$] and the homogenate was centrifuged at 10000 x g (4°C) for 20 minutes. The supernatant was further centrifuged at 105000 x g (4°C) for 90 minutes and the resultant pellet was suspended in ice-cooled 100 mM potassium phosphate buffer (pH 7.4) and recentrifuged at 105000 x g (4°C) for 90 minutes. The pellet (microsome fraction) was suspended in ice-cooled 100 mM potassium phosphate buffer (pH 7.4) (protein concentration ca. 40 mg/ml, as determined with Pias BCA Protein Assay Kit) to provide an enzyme preparation.

Test Example 2 Preparation of a human enzyme

Human hepatocarcinoma cells HepG2 (ca. 1×10^9 cells) grown in Dulbecco's modified Eagle's medium containing 10% fetal calf serum (37°C, 5% CO_2) were suspended in 10 ml of ice-cooled buffer [100 mM potassium phosphate buffer (pH 7.4), 30 mM nicotinamide, 2.5 mM $MgCl_2$] and disrupted by sonication (30 seconds x 2). From the sonicate, a microsome fraction was separated by the same procedure as described in Test Example 1. This fraction was

suspended in ice-cooled 100 mM potassium phosphate buffer (pH 7.4) (protein ca. 4 mg/ml) to provide an enzyme preparation. The results are shown below.

[Table 1]

Squalene synthase inhibitory activity (in vitro)

		Rat enzyme IC_{50} (μM)	Human hepG2 enzyme IC_{50} (μM)
Example 1	I	43%[1)]	
	II	0.026	0.011
Example 2	I	7.7	
	II	0.017	0.011
Example 3	I	15.8%[1)]	
	II	0.022	0.0086
Example 8		0.029	0.019
Example 9		0.041	0.022
Reference Example 1		0.067	0.020

1) % Inhibition at 10^{-5} M

Formulation Examples

The squalene synthase inhibitor composition comprising the optically active 4,1-benzoxazepin-2-one derivative (I) or its salt as an active ingredient for the therapy of hypercholesterolemia in accordance with this invention can be provided typically in the following formulations and dosage forms.

1. Capsule

(1) Compound of Example 5	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
Each capsule contains	180 mg

The whole amounts of (1), (2) and (3) and one-half

amount of (4) are blended and granulated. To the granulation is added the balance of (4) and the whole composition is filled in a gelatin capsule.

2. Tablet

(1) Compound of Example 5	10 mg
(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(4) Magnesium stearate	5 mg
Each tablet contains	230 mg

The whole amounts of (1), (2) and (3), 2/3 amount of (4) and 1/2 amount of (5) are blended and granulated. To the granulation is added the remainders of (4) and (5) and the whole composition is compressed into a tablet.

3. Capsule

(1) Compound of Example 9	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
Each capsule contains	180 mg

The whole amounts of (1), (2) and (3) and one-half amount of (4) are blended and granulated. To the granulation is added the balance of (4) and the whole composition is filled in a gelatin capsule.

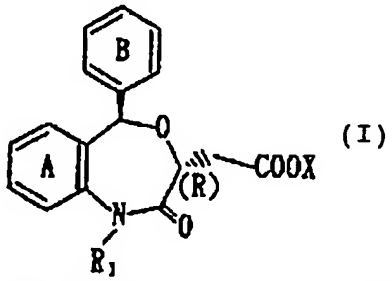
4. Tablets

(1) Compound of Example 9	10 mg
(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
Each tablet contains	230 mg

The whole amounts of (1), (2) and (3), 2/3 amount of (4) and 1/2 amount of (5) are blended and granulated. To the granulation are added the remainders of (4) and (5) and the whole composition is compressed into a tablet.

CLAIM

1. An optically active 4,1-benzoxazepin-2-one derivative of the following formula (I):



(I)

wherein R_1 represents a lower alkyl group; X represents a hydrogen atom or a metal ion; ring A represents a phenyl group substituted with halogen; ring B represents a phenyl group substituted with a lower alkoxy.

2. The optically active 4,1-benzoxazepin-2-one derivative according to claim 1 wherein said lower alkyl group is isobutyl or neopentyl.

3. The optically active 4,1-benzoxazepin-2-one derivative according to claim 1 wherein said metal ion is sodium ion or potassium ion.

4. The optically active 4,1-benzoxazepin-2-one derivative according to claim 1 wherein said halogen is chlorine.

5. The optically active 4,1-benzoxazepin-2-one derivative according to claim 1 wherein said lower alkoxy is methoxy or ethoxy.

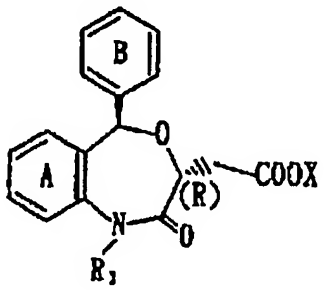
6. The optically active 4,1-benzoxazepin-2-one derivative according to claim 1 which is (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium salt.

7. The optically active 4,1-benzoxazepin-2-one derivative according to claim 1 which is (3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium

salt.

8. The optically active 4,1-benzoxazepin-2-one derivative or salt according to claim 1 which is (3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium salt.

9. A squalene synthase inhibitor composition comprising an optically active 4,1-benzoxazepin-2-one derivative of the following formula (I) as an active ingredient.



(I)

wherein R_1 represents a lower alkyl group; X represents a hydrogen atom or a metal ion; ring A represents a phenyl group substituted with halogen; ring B represents a phenyl group substituted with a lower alkoxy.

10. The squalene synthase inhibitor composition according to claim 9 wherein said lower alkyl group is isobutyl or neopentyl.

11. The squalene synthase inhibitor composition according to claim 9 wherein said metal ion is sodium ion or potassium ion.

12. The squalene synthase inhibitor composition according to claim 9 wherein said halogen is chlorine.

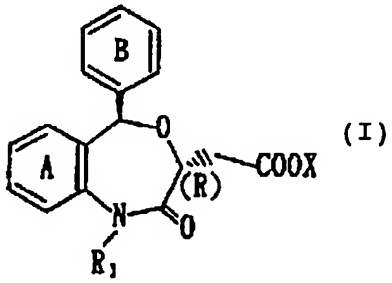
13. The squalene synthase inhibitor composition according to claim 9 wherein said lower alkoxy is methoxy or ethoxy.

14. The squalene synthase inhibitor composition according to claim 9 wherein said active ingredient is (3R,5S)-7-chloro-5-(2,3-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium salt.

15. The squalene synthase inhibitor composition according to claim 9 wherein said active ingredient is (3R,5S)-7-chloro-5-(2,4-dimethoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium salt.

16. The squalene synthase inhibitor composition according to claim 9 wherein said active ingredient is (3R,5S)-7-chloro-5-(4-ethoxy-2-methoxyphenyl)-1-neopentyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepine-3-acetic acid or its sodium salt.

17. An antimycotic composition comprising an optically active 4,1-benzoxazepin-2-one derivative of the following formula (I) as an active ingredient.



(I)

wherein R_1 represents a lower alkyl group; X represents a hydrogen atom or a metal ion; ring A represents a phenyl group substituted with halogen; ring B represents a phenyl group substituted with a lower alkoxy.

18. A method for the prophylaxis or treatment for hypercholesterolemia or coronary sclerosis in a mammal which comprises administering a pharmaceutical effective amount of the compound claimed in claim 1, to a mammal in need thereof.

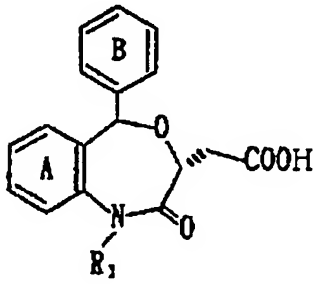
19. A method for the prophylaxis or treatment for mycotic diseases in a mammal which comprises administering a pharmaceutical effective amount of the compound claimed in claim 1, to a mammal in need thereof.

20. Use of the compound claimed in claim 1, for the manufacture of a medicament to be used as a prophylactic

or therapeutic drug for hypercholesterolemia or coronary sclerosis.

21. Use of the compound claimed in claim 1, for the manufacture of a medicament to be used as a prophylactic or therapeutic drug for mycotic diseases.

22. A method for producing the compound claimed in claim 1 which comprises (i) subjecting a compound of the following formula:



wherein all symbols are of the same meaning as defined in claim 1 to optical resolution and (ii), if necessary, dissolving the resultant compound and an alkali metal hydroxide in an alcoholic solvent.

23. The method according to claim 22, which comprises reacting the compound with an optically active amine.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 95/00148

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D267/14 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 567 026 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 27 October 1993 cited in the application see the whole document, particularly pages 102, 103, 105, 152, 155, 156 and pages 146-150, examples 114, 118 and 121 ---	1-23
A	CHEMICAL ABSTRACTS, vol. 97, no. 15, 11 October 1982 Columbus, Ohio, US; abstract no. 127667f, page 731; cited in the application see abstract & JP,A,82 035 576 (TAKEDA CHEMICAL INDUSTRIES, LTD.) -----	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1995	16.06.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I national application No.
PCT/JP 95/00148

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 95/00148

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-567026	27-10-93	AU-B-	3700393	21-10-93
		CN-A-	1083481	09-03-94
		JP-A-	6239843	30-08-94